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Membrane lipid environment: Potential modulation of chemokine receptor function

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ABSTRACT

Migration of leukocytes is typically mediated by G protein-coupled receptors (GPCRs) upon activation by specific ligands that range from small peptides, chemokines to a variety of lipidic molecules. The heptahelical receptors are highly dynamic structures and the signaling efficiency largely depends on the discrete contact with the ligand. In addition, several allosteric modulators of receptor activity have been reported, which do not induce migration by themselves. Another important mechanism modulating the activity of GPCRs is their local environment. Not only the membrane lipid composition influences the activity, but also direct binding of lipids, in particular cholesterol, was shown to alter receptor signaling properties. Recent findings indicate that also chemokine receptor activity is modulated by membrane lipids. In this short review we discuss this new paradigm and potential consequences for chemokine-induced migration.

1. Introduction

The chemokine family is comprised of about 50 structurally related proteins that mainly orchestrate the migration and recruitment of leukocytes in health and disease [1,2]. Typically, chemokines signal through specialized G protein-coupled receptors (GPCRs), primarily of the G_i type, to guide cell migration. However, chemokines are also able to bind to a small group of atypical chemokine receptors (ACKRs) which are considered not to initiate classical signaling pathways but to scavenge chemokines. Thereby, ACKRs contribute to the formation and maintenance of chemokine gradients or to eliminate chemokines during the resolution of inflammatory responses [3,4]. Chemokine receptors as any other GPCR are complex signaling machines that are embedded in the cell membrane. The lipid bilayer of a cell membrane is composed of two apposing leaflets, forming a dynamic two-dimensional liquid surrounding the transmembrane proteins [5]. The lipid composition of the plasma membrane together with the propensity to segregate lipids and proteins laterally are key parameters in controlling signal transduction across the membrane. Structurally, chemokine receptors span the plasma membrane sevenfold whereby the transmembrane α-helices are connected by three extracellular and three intracellular loops. The intracellular C-terminus follows an eighth α-helix that arranges parallel to the inner leaflet of the membrane. Notably, certain, but not all, chemokine receptors are palmitoylated at their C-terminus anchoring the eighth α-helix into the lipid bilayer [3]. The extracellular N-terminus is linked through a disulfide bond to the third extracellular loop and is considered to control chemokine binding and ligand specificity [6,7]. In general, the basic core domain of the chemokine interacts first with the negatively charged N-terminus of the receptor while the chemokine's N-terminus inserts into the ligand binding pocked defined by the seven transmembrane bundle of the receptor, referred to as chemokine recognition site (CRS) 1 and 2 [7]. Recent chemokine:receptor structures revealed more extensive interaction interfaces between the receptor and its ligand than originally anticipated [7–10]. Binding of a chemokine to its canonical chemokine receptor leads to the rearrangement of the transmembrane helices resulting in profound conformational changes across the plasma membrane. The altered conformations can be defined as active or inactive states based on their ability to couple to downstream signaling molecules. In their active states, GPCRs catalyze the exchange of GDP for GTP on the α-subunit of the heterotrimeric G protein. The GTP-loaded Gα-subunit subsequently dissociates from the Gβγ-heterodimer whereby both the Gα-subunit as well as the Gβγ-heterodimer can trigger downstream effectors. Notably, both the Gα and the Gγ-subunit are anchored in the inner leaflet of the membrane through lipidation [11]. Crystal structures of β-adrenergic receptors in active and inactive states revealed that the largest conformational change upon receptor activation is an outward movement of transmembrane helix 6 with subtle changes in transmembrane helices 5 and 7 [12–14]. Using a comprehensive shotgun mutagenesis approach to identify critical residues in CXCR4 to transmit signals revealed that a 'hydrophobic bridge' on helix 6 is essential for CXCL12 mediated signal propagation [15]. Remarkably, this 'hydrophobic bridge' motif on helix

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6 located in the middle of the plasma membrane is highly conserved among GPCRs and seems to coordinate GPCR signaling in general [15]. As major parts of chemokine receptors are embedded within the membrane and as several down-stream signaling molecules are lipidated, it is comprehensible that the membrane environment and the lipid composition proximal to the receptor impacts on its function [16]. In addition, ligands of a given receptor can bind and activate it with different affinities (potencies) and efficacies. The differences in ligand potency and efficacy are described on a linear scale from inverse, partial to full agonists [17,18]. More recently, biased signaling of GPCRs, including chemokine receptors, was proposed, where a signaling bias can depend on the ligand, the receptor and on the cellular context of the receptor [19,20]. As neither molecular mechanisms of potential signal transduction elicited by ACKRs are being understood nor a crystal structure of a single ACKR has been solved yet, this review article focuses on classical chemokine receptor functions in the context of their lipid environment. Consequences of altered cholesterol levels in disease such as atherosclerosis and its influence in modulating chemokine functions have been discussed elsewhere [16].

2. Chemokine receptors embedded in a compartmentalized membrane

Chemokine receptors are integral membrane proteins and transmit signals across membranes, primarily the plasma membrane. The plasma membrane is a semipermeable barrier that demarcates the intracellular milieu from the extracellular environment. Amphipathic lipids, particularly phospholipids and sphingolipids, are the major building blocks of these lipid bilayers [5]. Thereby, the hydrophilic heads of the lipids interact with the extra- and intracellular aqueous environment, whereas the hydrophobic fatty acyl lipid tails associate together. Notably, the membrane fluidity, which is determined by the fatty acyl groups of the amphipathic lipids and their degree of saturation, enables certain lateral movement and concentration of (trans)membrane and membrane associated proteins. Recent studies not on chemokine receptors, but on other GPCRs revealed that membrane phospholipids are able to modulate receptor oligomerization [21] and allosteric activation [22]. As an essential membrane component in mammalian cells, cholesterol not only contributes to maintaining the semipermeable membrane barrier function, it also regulates the membrane fluidity and bilayer thickness, is involved in the formation of membrane microdomains and consequently, the local cholesterol content modulates the functions of membrane proteins [5,23–25]. Cholesterol interacts preferentially with saturated acyl chains of sphingolipids and phospholipids, and through its puckered four-ring structure, confers special biophysical properties, which increase cohesion and packing of neighboring lipids and proteins. Therefore, cholesterol can directly or indirectly influence GPCR functions. Direct effects are those that arise from cholesterol physically interacting with the GPCR, whereas indirect effects are caused by alterations in the physico-chemical properties of the membrane that embeds the receptor. Hence, changes in cholesterol levels affect the lateral mobility of both the GPCR within the lipid bilayer, as well as the lipidated signaling molecules. In fact, many GPCRs including CCR5 are palmitoylated at the C-terminus [26,27]. Palmitoylation was recently shown to be a prerequisite for the dimerization-dependent raft association of rhodopsin [28]. Most prominent lipidated signaling molecules down-stream of the GPCR are the Gα- and the Gγ-subunits of the heterotrimeric G protein itself. The Gα-subunit is modified at the C-terminus with the saturated fatty acid palmitic acid, whereas the Gγ-subunit is prenylated [11,29]. Similarly, members of the Src family kinases and cytoskeleton regulating proteins are also lipidated [30,31].

3. Role of cholesterol in chemokine receptor oligomerization

The importance of cholesterol becomes obvious by the fact that all chemokine receptors, which have been crystalized so far, were solubilized and purified in the presence of this lipid [8–10,32]. Hence the presence of cholesterol seems to control the receptor's stability. In line with this, cholesterol was shown to enhance CXCL12 binding of solubilized CXCR4 [33]. Notably, the presence of cholesterol in the crystal structures of chemokine receptors has not been reported, neither for CXCR4 nor for CCR5. However, a direct physical interaction between cholesterol and the GPCR was noted in the crystal structure of the β_2-adrenergic receptor (β_2AR) [34] and the P2Y12 receptor [35], where two cholesterol molecules were associated with a receptor monomer. In addition, crystals derived from inverse agonist-bound β_2AR revealed a symmetric arrangement of dimeric receptors, where roughly 70% of the dimeric interface was mediated by ordered lipids consisting of six cholesterol and two palmitic acid molecules per receptor dimer [36]. In the case of the A_{2A} adenosine receptor, three cholesterol molecules were reported to intercalate at the receptor dimer interface [37]. Sequence analysis among a large panel of class A GPCRs led to the identification of a 'consensus cholesterol binding motif' present in 44% of the analyzed GPCRs [34]. However, none of the chemokine receptors possess such a 'consensus cholesterol binding motif'. Nonetheless, *in silico* molecular docking simulations revealed the presence of a cholesterol binding pocket in CXCR4 and CCR5 [38].

It is widely accepted that chemokine receptors can form dimers or oligomers [39,40]. However, GPCRs can fully activate heterotrimeric G proteins in a monomeric state [41]. Dimers of chemokine receptors are presumably formed during biosynthesis and are detectable in small vesicles during transport from the endoplasmic reticulum to the Golgi apparatus [42,43]. Obviously, chemokine receptor dimerization during biosynthesis happens in the absence of ligands. Chemokine receptors can form homo- as well as hetero-mers and the arrangement of dimers within oligomeric structures with and without direct physical interaction has been discussed previously [39]. The functional consequences of chemokine receptor dimerization and/or oligomerization seems to vary among different chemokine receptors and GPCRs. In fact, allosteric inhibition, as well as cooperative and synergistic activation of chemokine receptor dimers and/or oligomers have been reported for various receptor pairs [39,40]. An example with remarkable molecular details of how receptor dimerization and oligomerization can modulate receptor signaling and function has recently been identified for the chemokine receptor CCR7 [16,19]. There, a hydrophobic interaction surface proximate to the NPXXY motif within the transmembrane domain 7 has been identified to be critical for CCR7 homo-dimerization. Mutation studies revealed that reducing this hydrophobic contact surface of CCR7 impaired receptor dimerization, whereas enlarging the hydrophobic interaction surface promoted receptor dimerization [19]. Functionally, cell lines expressing CCR7 mutants with a low dimerization propensity migrated inefficiently towards their ligands CCL19 and CCL21, whereas cells expressing dimerization-prone CCR7 showed a significantly better chemotactic responsiveness [19]. Mechanistically, CCR7 oligomers in their inactive state interacted with the tyrosine kinase Src, whereas dimerization-defective receptor mutants hardly interacted with Src. Consequently, chemokine binding to oligomeric CCR7 activated receptor-associated Src resulting in CCR7 tyrosine phosphorylation within the highly conserved DRY-motif located at the transition between transmembrane domain 3 and the second intracellular loop of the receptor [19]. Tyrosine-phosphorylated CCR7 served as docking site for further down-stream signaling molecules harboring SH2-domains that contributed to enhanced signaling and more efficient cell migration [19]. Of note, CCR7 oligomerization on human monocyte-derived dendritic cells was enhanced if cells encountered a danger signals. Particularly inflammatory signals including prostaglandin E_2 enhanced CCR7 oligomerization and promoted cell migration. Interestingly, the same inflammatory signals down-regulated genes of the cholesterol metabolism [19]. Pharmaceutical intervention using cholesterol-lowering drugs revealed that moderately reducing cellular cholesterol levels enhanced CCR7 oligomerization and cell migration [19]. Notably, harsher treatment of cells with cholesterol-

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